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EMERGENT PROPERTIES FOLLOWING BRAIN INJURY: THE CLAUSTRUM AS A MAJOR COMPONENT OF A PATHWAY THAT INFLUENCES NOCICEPTIVE THRESHOLDS TO FOOT SHOCK IN RATS[1]

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Summary.—Flinch (pain) thresholds for electric current delivered to the feet were correlated with the amount of necrosis within the diencephalon and telencephalon for rats in which seizures had been induced by lithium and pilocarpine about two months before the testing. The shared variance of the quantitative damage within the claustrum, the anterior part of the paraventricular nucleus of thalamus, (central) mediodorsal thalamus, and lateral amygdala (ventromedial part) explained 81% of the variance in the nociceptive (flinch) thresholds. A primary role of the claustrum within the neuropathways that mediate the response to the interoceptive and "painful" characteristics of stimuli is indicated. The concept of primary pathways versus "emergent" pathways subsequent to excitotoxic damage within the neuromatrix is discussed.

A multifocal approach to brain function is considered ecologically relevant in light of the typical clinical manifestations of traumatic or idiopathic brain injury (Persinger, Bureau, Kostakos, Peredery, & Falter, 1993). The behavioral-brain correlates for the consequences of this form of acquired brain injury have supported the theoretical concept that multicontributory structures within diverse regions and involving parallel processing are the substrate for most behaviors. Our results (Persinger, Bureau, & Peredery, 1994) have also reinforced the concept of a neuromatrix that is optimally seen when the smallest structurally homogeneous (Paxinos & Watson, 1986) mosaics within the brain are discriminated and employed in quantitative analyses.

This approach results in two major implications. First, averaging cytological damage within larger, traditional perimeters such as the "central amygdala" or the "mediodorsal thalamus" is overinclusive and dilutes the particular contribution of subnuclear components due to averaging. Secondly, some behaviors may not be associated with specific nuclei but would instead be associated with a system composed of several structures. The elements within a system would not be indispensable (Neafsey, Terreberry, Hurley, Ruit, & Frysztak, 1993) and could be substitutable.

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From this perspective the specific structures that contribute to the neuromatrix with which the response is associated may not always be accessed by single lesions because they do not affect the aggregate properties of the system. Single lesions usually attenuate rather than eliminate the occurrence of a behavior. Often the residual variance from other components of the neuromatrix that contribute to this behavior would be allocated to 'error' variance or "individual differences." On the other hand, excitotoxic stimulation excessively activates intrinsic neuropathways and, without appropriate attenuation of this hyperactivity, results in selective necrosis within all of the structures that compose these "functional circuits." Numerical inferences of damage within these components accommodated more than 80% of the variability in the measurements of classic behaviors (Persinger, Bureau, & Peredery, 1994).

Perhaps the most novel concept that emerges from a neuromatrix approach to brain organization is that a response may be associated with a specific structure whose role is recondite or masked during periods of "normal" stable states that precede an acquired brain injury. Following functional reorganization of the neuromatrix, structures could be recruited into different patterns or matrices that would be associated with quite different behaviors. The "reorganization" could be subsequent to changes that could range from large areas of frank neuronal damage (as inferred by computerized tomography, CT) to alterations in the pattern of different neurotransmitters sequestered by synapses within the primary systems that maintain the "normal" stable states (as inferred by differential responses, relative to normal animals, to drugs that are sequestered by specific subtypes of receptors).

The pursuit of this approach also requires a shift in methodology. Until the intrinsic algorithms are discerned, an empirical inductive procedure would be required. We have found that multiple regression analysis is an optimal statistical tool to isolate those structures whose proportion of damage due to excitotoxic lesions contribute to the numerical variability of a measured behavior. The following experiment was designed to discern whether structures, not previously implicated, might contribute to the fundamental process of nociception. Nociception is defined as the detection of and response to stimuli that could result in tissue damage and can be considered an essential capacity for adaptability. Within the normal human, this phenomenon is experienced and reported as pain.

Method

Subjects

A total of 14 male, 150-day-old Wistar albino rats (obtained from Charles River, Quebec) served as subjects. This number was selected be-

cause our predicted effect size required > 10 rats to be statistically significant at $p < .001$.

Procedure

At approximately 80 days of age and following approval of the protocol by the university's Animal Care Committee, the rats were injected subcutaneously with one of four combinations ($n = 3$ or 4 rats/treatment) of lithium chloride (LiCl) and then pilocarpine (the reverse administration of the two drugs does not evoke seizures): (a) 1 mEq/kg of LiCl followed 4 hr. later by either 10 mg/kg or 30 mg/kg of pilocarpine, (b) 1 mEq/kg of LiCl followed 24 hr. later by 30 mg/kg of pilocarpine, and (c) 3 mEq/kg of LiCl followed 24 hr. later by 30 mg/kg of pilocarpine. The temporal-dosage parameters were derived from our initial studies (Persinger, Makarec, & Bradley, 1988).

All rats displayed the typical rearing, forelimb clonus and falling (similar to a Type IV kindled myotonic seizure) within about 20 to 50 min. and were then injected subcutaneously with 25 mg/kg of acepromazine (Atravet) to facilitate survival. [Rats that have not displayed the overt limbic motor seizures have never displayed any discriminable neurohistological damage as defined by 400× light microscopy.] During the recovery the rats were maintained in group housing for about 30 days. They were then housed singly within climate controlled rooms (temperature within 1° C of 20° C); Purina rat chow and water were available *ad libitum*. The light:dark cycle was 12:12; the dark cycle began at 19:30 hr.

Seventy days after the induction of the seizures, each rat was tested singly for its nociceptive threshold during the mid-light cycle. The rat was placed within a standard Plexiglas chamber that contained a floor composed of metal rods (Fleming, Persinger, & Koren, 1994). The intensity of the electric shock was slowly increased (from zero) through an A-615-C Master Shocker (Lafayette Instrument Co.) until the rat displayed a clear flinch; this movement was qualitatively distinct and exhibited 100% interrater agreement. After 30 sec., the electric shock was increased by 1 increment and then decreased quickly until the rat did not flinch (total time required about 2 sec.). The threshold, in mA, was recorded. The rat was then returned to its home cage.

Within two days the rats were decapitated. The brains were removed and fixed in ethanol-formalin-acetic acid. After processing (Persinger, 1979), the cerebrums were sectioned by a microtome set at 10 micrometers. Every 80th section was then stained with toluidine blue O and examined by light microscopy at 100× and 400×. Each of *all* of the structures that are delineated by Paxinos and Watson (1986), within the diencephalon and the telencephalon (as far rostrally as the anterior commissure) was examined by an experienced histopathologist (second author). The determination of necrosis

or damage, described in detail elsewhere (Persinger, *et al.*, 1994) involved estimating the percentage of the structure (without knowing the treatment history of the brain) that exhibited neuronal dropout or gliosis. Stated briefly, each structure on each slide received a rating of the proportion of damage (0 through 10). The average value for each structure (that involved two to four slides) was computed and then multiplied by 10 (% damage). According to a random sample of neurons within 10 separate nuclei within the thalamus and amygdala ($n=20$ cases, each), the correlation between the scores for percentage damage and the actual numbers of viable neurons (measured at 1000× within several visual fields) within a given structure ranged from 0.8 to 0.9.

The values for the extent of damage within each of the approximately 100 specific structures that are typically affected by the consequence of the lithium/pilocarpine-induced seizures (Bureau, Peredery, & Persinger, 1994) as well as the nociceptive (flinch) thresholds (ascending and descending values) for each rat were loaded onto a Vax 4000 computer. The means, standard deviations, and skewness for the percentage of damage within each structure for all 14 rats were obtained (the extent of damage was comparable to that in previous studies). To minimize the potential distorting effects from outliers nonparametric (Spearman *rho*) and parametric (Pearson *r*) correlations were performed between the indices of damage for each structure and the average of the ascending and descending nociceptive threshold. This average was employed for these analyses because there was no statistically significant ($p>.05$) difference between the two values ($t=1.59$), and they were strongly correlated ($r=.95$, $p<.001$).

Those structures that were significantly ($p<.01$) correlated with the flinch thresholds for *both* the parametric and nonparametric correlations were selected for factor analyses (PA1). To identify potential recondite sources of variance that were only evident once the primary sources of variance were removed, multiple regression analysis was completed. The flinch threshold was employed as the dependent variable. Given the required effect size and the sample size, we set the maximum number of variables that could enter the equation equal to 3. All analyses involved SPSS software.

Because the ratings of damage in one structure, the claustrum, displayed the first and strongest quantitative association with flinch threshold, this structure was evaluated in detail for each brain. The average numbers of astroglia, microglia, oligodendroglia, and neurons per microscopic field (1000×) for a total of eight fields within the left claustrum and a total of eight fields within the right claustrum were calculated. The numbers of neurons were restricted to those soma for which the nucleus was evident. There were two classifications of neurons, normal and abnormal. Abnormal were

defined as those neurons that showed distinct chromolytic characteristics; the interrater agreement for this designation exceeded .90.

Results

The mean and standard deviation for the flinch (nociceptive) threshold were 0.15 and 0.05 mA, respectively; for comparison the mean and standard deviation for control, age- and weight-matched male rats ($n=30$) were 0.05 and 0.02 mA, respectively. Only four structures met the criterion of exhibiting *both* statistically significant ($p<.01$) nonparametric and parametric correlations with the flinch threshold. These structures were the claustrum, the lateral amygdala, ventromedial part, the paraventricular nucleus of the thalamus (anterior part), and the central portion of the medial dorsal thalamus. The means and standard deviations (in parentheses) for all 14 rats for the percentage of each structure's area that exhibited microscopic damage were, respectively, 35 ($SD=38$), 79 ($SD=23$), 7 ($SD=17$), and 81 ($SD=24$). The means and standard deviations for the other approximately 100 structures for which damage was not significantly correlated with the nociceptive threshold were comparable to those of previous studies (Bureau, *et al.*, 1994) and consequently are not presented.

The results of the factor analysis indicated that all four of these structures loaded upon the same factor; the factor loadings are shown within the insert in Fig. 1. The scattergram for the relationship between the standardized factor score for these four structures and the nociceptive or flinch threshold in mA is also shown in Fig. 1. The correlation of .90 was statistically significant ($p<.001$).

To discern potentially hidden or iterative relationships the results of the step-wise multiple regression were scrutinized. The multiple R was .93 ($F_{3,10}=20.35$, $p<.001$) and the standard error of the estimate was .02 mA. The partial slopes and standard errors of these partial regression coefficients for the three structures (in order) that entered the equation were for the claustrum .009 ($SE=.002$), the paraventricular nucleus of the thalamus .014 ($SE=.004$), and the gustatory nucleus of the thalamus .003 ($SE=.001$); the constant for the equation was .10. The change in adjusted-r^2 for the first two variables were for the claustrum 50% and for the paraventricular nucleus 22%. The correlation (r) between the observed values and the predicted values derived from the equation was .93.

To discern the specific cytological profile within the claustrum that constituted the necrotic characteristics which were correlated with the elevation in nociceptive threshold in these rats, Spearman *rho* correlations were completed between the rating scale for necrosis and (1) the averages of the numbers of different types of glial cells, (2) the two types of neurons, and (3) the averages of the ratio of each of the three type of glial cells and abnormal

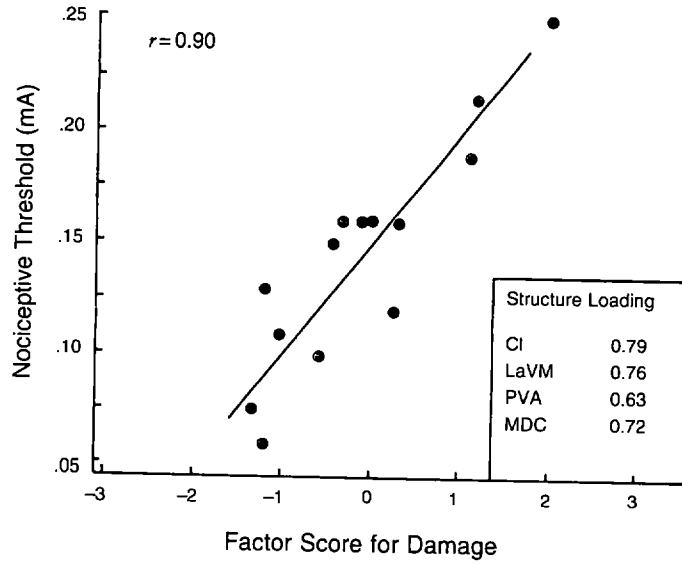

FIG. 1. Scattergram of the relationship between the flinch threshold to electric shock and the factor score of the amount of damage within the claustrum, lateral amygdala (ventromedial) and the (anterior) paraventricular nucleus and mediodorsal (central) nucleus of the thalamus. The inset indicates the factor loadings of each structure.

neurons to the total numbers of normal neurons per field. The means and standard deviations (in parentheses) for numbers of types of cells per mm-squared were for normal neurons 272 ($SD=53$), chromolytic neurons 359 ($SD=66$), nuclei of oligodendroglia 97 ($SD=33$), nuclei of astroglia 228 ($SD=34$), and microglia 35 ($SD=23$).

Fig. 2 shows examples of claustra with different amounts of neuronal dropout from four different rats that displayed the range of nociceptive thresholds. Fig. 2A is from a rat that displayed no discernable microstructural alterations. Fig. 2B and 2C show claustrums from rats (intermediate elevation of nociceptive threshold) that contained infiltration of glial cells and neuronal dropout. Fig. 2D, from a rat that showed one of the maximum values for threshold, is indicative of the near complete loss of intermediate-size neurons.

The results of the nonparametric correlations between the mean necrosis score per claustrum and the average cytological profile were clear. The damage scores were not significantly associated with either the numbers of the different glial cells or neurons per 1000× field or the ratio of the classes of glial cells per total numbers of neurons per 1000× field. However, the rating was significantly correlated ($rho=.82$, $p<.001$) with the ratio of chro-

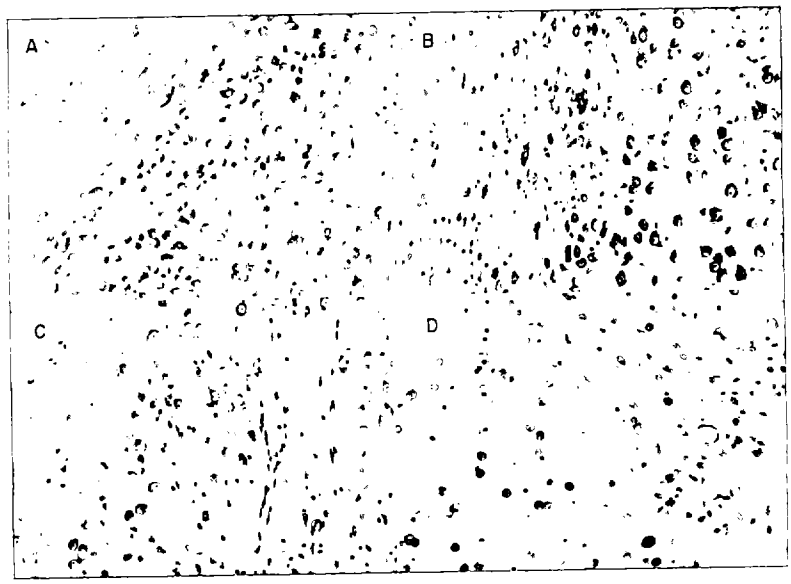

FIG. 2. Photomicrographs of the same regions of the claustrum for four different rats at 400× (Toluidine blue 0). A through D indicate increasing scores along the scale of damage as discerned by counts and by qualitative estimates.

molytic neurons to the numbers of normal neurons. The mean and the standard deviation for this ratio were 1.33 and 0.13, respectively.

Although the sample size was only 14 brains, factor analysis (PA1) extracted only one factor upon which the necrotic rating for the claustrum, the ratio of chromolytic neurons and the nociceptive threshold all loaded with *r* values between .75 and .95. When the nociceptive threshold in mA was employed as the dependent variable and the glial and neuronal indices were employed as predictors, only the ratio of chromolytic neurons (partial beta = .78) and ratio of oligodendroglia cells (partial beta = −.50) entered the equation.

DISCUSSION

The behavioral consequences from a single lesion by extrinsic intervention within a specific structure or from multivariate damage within a field of brain tissue by intrinsic stimulation should be complimentary and hierarchical. We predict that the twenty-first century perspective will view the single lesion study as a special condition of the multivariate perspective. The comparison might be analogous to the shift in paradigm during this century that did not eliminate Newtonian mechanics but placed it as one subset of more explanatory, relativistic frameworks.

We have suggested that techniques that induce autolesions could reveal

the intrinsic primary organization of nuclei that form the functional matrices as well as the "emergent" organizations (subsequent to damage) within the brain. Metaphorically, this change would be analogous to the reorganization of the "same" elements within a kaleidoscope which results in a different functional (spatial) relationship between the elements and a different pattern or aggregate structure.

Experimental procedures that can change the "wiring" of the genetically normal brain are essential if we are to isolate the intrinsic microstructural patterns that determine the "constants" for the detections of and the responses to the myriad of potential stimulus patterns within the environment. Constants and fundamentals within a system cannot, by definition, be discerned within the system. Their detection requires the type of contrast that can only emerge from an alternative tensor or different frame of reference.

If clinical neuroscience continues to proscribe to the principle that structure dictates function and to its corollary that microstructure dictates microfunction, then the same neuronal elements could be involved with qualitatively different behaviors. This possibility has significant implications for the interpretation of the intervention and symptoms of patients who have sustained multiple petechial (microfocal) partial neuronal loss secondary to a closed (traumatic) brain injury (Persinger, 1995) and who experience subsequent diffuse pain for years. The etiology is often attributed to "depression," psychiatric innuendo, or related defaults for idiopathic sources.

The results of the present study support the general metaphor that multifocal structures within different portions of the brain are involved with discrete behaviors. Although the significant correlation between the flinch threshold and the amount of damage within the claustrum, paraventricular thalamus, mediodorsal thalamus, and lateral amygdala could have been associated with different sources of variance, the results of the factor analysis indicated that the quantitative amount of damage within these structures was derived from a single source of variance. The subsequent entry of the paraventricular nucleus within the multiple regression analysis after the shared variance with the claustrum had been removed (by definition) suggests that the former structure added additional variance that was not associated with the primary factor.

That the involvement of these structures was related to spurious numerical artifacts is unlikely because the means and standard deviations for these variables were not extreme and were comparable to those for many other structures that were not significantly associated with nociceptive thresholds. The empirical result that the amount of damage within only two structures (claustrum and paraventricular nucleus) explained 72% of the variance in the flinch threshold, even though any of the structures could have poten-

tially entered the equation, also supports the reliability of the effect. Even from an extremely conservative statistical perspective, the probability that the relationship between claustral damage and nociceptive threshold was due to chance was less than one in ten thousand. Because only a dozen other structures exhibited discernable damage, i.e., were included as potential independent variables, the probability that claustral association was due to chance is quite minimal.

A causal relationship between the attenuation of the detection of a painful stimulus (as reflected by a higher flinch threshold) and damage to the paraventricular nucleus of the thalamus would be consistent with traditional interpretations of function. This structure has been implicated for both arousal and intrinsic response to sensory afferents. The paraventricular nucleus is a component of the midline thalamic group that facilitates the integration of activity within several cerebral regions. The anterior portion of the paraventricular nucleus is also a source of significant afferents to the amygdala (Bentivoglio, Balercia, & Kruger, 1991; Groenewegen & Berendse, 1994) which in turn sends powerful inputs into the medial dorsal thalamus.

However, the involvement of the claustrum is by far the most important observation and is compatible with our approach that autolesions of primary neuropathways by excitotoxic techniques can indicate the importance of nuclei whose role is normally masked in the unchanged brain or whose functional significance varies when different neuromatrices emerge after multifocal brain injury. Although direct connections between the claustrum and the insula were not addressed in a recent review (Augustine, 1996), the location of the claustrum (between the insula and the lateral amygdala) would be an ideal interface for a modulator of affective polymodal afferents as they are accessed or recruited into afferents of the anterior cingulate cortex (Crosby, Humphrey, & Lauer, 1962). Because the claustrum extends ventrally towards the lateral amygdala and (in humans) is coextensive with the putamen, somatoaffective functions have been implied as well (Crosby, *et al.*, 1962).

In addition to their shared variance with nociceptive thresholds, the lateral amygdala, mediodorsal (central part) nucleus, paraventricular nucleus and claustrum also share a similar pattern of cytoarchitecture. *Post hoc* examination of these structures indicated (qualitatively) that the cell loss was primarily within the parvocellular constituents of these nuclei. On the other hand the larger neurons were not, at least qualitatively, affected. Although the similarity of morphometric damage within the four major structures could imply vulnerability of neurons with shared receptor profiles or functions (inhibitory interneurons), we suggest that changes within another structure could have evoked the necrosis. The convergent candidate was the cingulate cortex.

There are at least two major components to nociceptive (pain) systems (Bentivoglio, Kultas-Ilinsky, & Ilinsky, 1993). The first involves the traditional (neurological) lateral pain pathway that transmits information regarding detection, localization, and discrimination of nociceptive stimuli from spinal inputs into the ventral tier of the thalamus before subsequent projection to the somatosensory cortices. The second pathway sends comparable information from the spinal cord through the periacqueductal grey into the medial thalamic and intrathalamic structures and then to the anterior cingulate. Lesions within the medial (and paraventricular) thalamus have been observed to prolong reaction times during exposures to heat stimuli (Vogt, Sikes, & Vogt, 1993).

Although the posterior cingulate receives major input from the hippocampal formation and from the parietotemporal cortices and is well known for its involvement with spatial orientation and spatial memory, the anterior cingulate appears to be primarily involved with the general domain of motivation. The anterior cingulate receives copious input from the amygdala and from the mediodorsal thalamus, the two major regions within which the correlative structures that predicted the elevated pain threshold were found. These results suggest that damage to the *claustrocingulate* pathways may attenuate the normal visceral and emotional responses which are usually evoked by noxious stimuli (Neafsey, *et al.*, 1993). Akinetic mutism and indifference to pain (Brown, 1988) following damage to this region would also be consistent with these results.

Whereas the dorsal portion of the anterior cingulate is primarily involved with the movements of the head and eyes, the ventral portion is more involved with the control of visceral functions that include cardiovascular tone, digestion, thermoregulation, reproductive behaviors, and immunocompetence. All of these domains have been shown to be affected, but after different periods of time, following the induction of seizures by lithium and pilocarpine (Bureau & Persinger, 1993; Harrigan, Bureau, Persinger, & Parker, 1994; Peredery, Persinger, Blomme, & Parker, 1992).

Although this study involved the quantitative association between the amount of damage within the structures and the nociceptive threshold, the interpretation does not necessarily indicate a direct (A--B) causal association. Behavior is due to the activity of neuronal networks, not to their absence (Persinger, 1995). Because at any given time those portions of the brain that are most metabolically active determine behavior, the strong association between brain and behavior in this study could be associated with secondary inhibitory regions that were disinhibited by the consequences of the seizure-induced damage. Support for this contention has been shown for aggressive behaviors in rats by Desjardins and Persinger (1995).

The behavioral consequences of lesions within an area are often the

converse of normal stimulation. If damage to these specific structures is associated with elevated nociceptive thresholds, then above-average neuroelectrical activity within the same (but intact) structures should be associated with reduced nociceptive thresholds and increased sensitivity to painful stimuli. We suggest that disruptions in emotional bonding in humans due to separation of significant people, which often produces the clinical correlates similar to opiate withdrawal (Panksepp, Normansell, Herman, Bishop, & Crepeau, 1988) could be associated with enhanced detectability of painful stimuli. Release from normal tonicity following trauma-induced dormancy of inhibitory interneurons (Bekenstein & Lothman, 1993) would also encourage a reduction in nociceptive thresholds.

In this context both the frequency and the interpretation of the stress-depression-pain cycle (Beutler, Engle, Oro-Beutler, & Daldrup, 1986) within patients who have sustained traumatic brain injuries but who exhibit only marginal neuropsychological impairment should be re-evaluated. Experiences of pain are psychological phenomena that emerge at the level of the cerebral cortices. Although normally these pathways are activated by spinal afferents in response to heterostasis within tissue, alterations within brain microstructure due to trauma would induce pain that is just as intense and perhaps even more incapacitating.

Primary involvement of the claustrocingulate pathways in the chronic alterations of pain thresholds suggests a possible neurosubstrate to the common clinical observations (Keefe & Gil, 1986) that chronic pain patients are characterized by a restricted lifestyle, overreliance upon family members (bonding), and dependence upon habit-forming analgesics. Dysfunction within the claustrocingulate pathway, particularly if modulated by the adjacent insular cortex, would support the hypothesis by Beutler, *et al.* (1986) that the inability to *express* intense affect is the common link between depression and pain.

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